

## Original Article

# Epidemiology of hepatocellular carcinoma in Japan

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Primary liver cancer, 95% of which is hepatocellular carcinoma (HCC), has ranked third in men and fifth in women as a cause of death from malignant neoplasm in Japan. Although the numbers of deaths and death rates from HCC increased until 2002 in Japan, annual deaths (34 089) and the death rate (27.0/100 000) from liver cancer decreased in 2003. Hepatitis C virus (HCV)-related HCC represents 75% of all HCC in Japan. The incidence of HCC without hepatitis B surface antigen (HBsAg) or anti-HCV accounted for 7–12% of HCC in Japan and half of non-B non-C-HCC was of unknown origin. Geographically, HCC is more frequent in western than eastern Japan, and the death rates from HCC in each prefecture correlate with the prevalence of anti-HCV, but not with HBsAg prevalence. Interferon therapy for chronic hepatitis C has reduced the risk factors for development of HCC, especially among patients with sustained response.

**Key words:** HCC, HBV, HCV, NASH, IFN

## INTRODUCTION

The three leading causes of death in Japan are malignant neoplasms, cardiovascular diseases, and cerebrovascular diseases. Since 1981, malignant neoplasms have been the leading cause of death in Japan. For the last 30 years, liver cancer has been the third leading cause of death from malignant neoplasms in men. In women, liver cancer has ranked fifth during the past decade.<sup>1</sup> Primary liver cancer can be classified into three types according to the cell from which the cancer arises, including hepatocellular carcinoma (HCC) and cholangiocellular carcinoma. HCC accounts for up 95% of all cases; therefore, "liver cancer" usually means HCC.<sup>2</sup>

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two major causes of HCC in Japan.<sup>3</sup> The increase in incidence of HCC in Japan, however, has largely been attributable to HCV infection and the increase of HCV in the general population during the last 50–60 years.<sup>4</sup>

## CHANGES IN NUMBERS OF DEATHS AND DEATH RATES FOR PRIMARY LIVER CANCER

Changes in annual numbers of deaths from primary liver cancer in different age groups between 1958 and 2003 are shown in Figure 1. The total number of deaths from HCC was stable, and fewer than 10 000 people/year until 1975 when numbers showed a sharp increase with years. The increase in 1995 was caused by the change in International Classification of Disease (ICD) codes from ICD-9 to ICD-10, which includes intrahepatic bile duct cancer (less than 5%). Peak numbers of deaths from HCC were in patients below the age of 69 years until 1999, when the peak age increased to over 70 years. Although numbers of deaths from HCC increased until 2002, the total numbers of deaths from HCC decreased to 34 089 in 2003.

Deaths rate from liver cancer by gender are shown in Figure 2. Rates were consistently higher in men than women. A sharp rise in death rates from primary liver cancer in men began in 1975, and a more gradual rise in women in 1980. Total age-adjusted death rates also increased until 2002 (27.5/100 000 people in 2002); however, it decreased to 27.0 in 2003. Therefore, number of deaths and the death rate from primary liver cancer decreased in 2003.

## AGE AND GENDER IN HCC

Changes in mean age of HCC patients and the male/female ratio every 2 years between 1984 and 2001 are shown in Figure 3. For 18 years, the mean age for females was higher than for males. The mean ages of males and females progressively increased from 1984–1985 to 2000–2001. As reported previously, however, it was unchanged in HBV-related HCC 1982 and 2003. Thus, this sharp increase originated in HCV-related HCC patients. The male/female ratio was 4.5 in 1983–1985 and 2.57 in 2000–2001 (Fig. 3). The ratio became clearly smaller, which indicates an

increase in female patients with HCC. This tendency is found in HCV-related HCC predominantly. The mean ages of male and female patients with HCC have increased each year (Fig. 3). The mean age of females was higher than for males throughout. The increase for female patients and the elevation of mean age are considered to increase because of HCV-related HCC.

#### **CHANGES IN ETIOLOGY OF HCC IN JAPAN**

A nationwide survey of primary liver cancer has been conducted every 2 years since 1968 by the Liver Cancer Study Group of Japan.<sup>5-10</sup> Five serologic surveys performed between 1990 and 2001 documented that most patients with HCC are positive for either hepatitis B surface antigen (HBsAg) or antibody to HCV (anti-HCV). Tests for HBsAg became available in 1975 and those for anti-HCV in 1990. HBsAg-positive cases of HCC constituted 42% of cases in 1977-1978, but only 15.5% in 2000-2001 (Fig. 4). In contrast, anti-HCV-positive cases of HCC have accounted for more than 70% of cases diagnosed in the last 10 years. Unknown origin and other cases of HCC have increased gradually and constituted 12.7% of cases in 2000-2001.

#### **NON-B, NON-C HCC IN JAPAN**

In cross-sectional studies conducted at the Shinshu University Hospital, HCV-related HCC has increased to become the majority of cases (72%). Non-B non-C HCC accounted for 7% of cases in 2003.<sup>3</sup> The survey of non-B non-C HCC was conducted by the Inuyama Hepatitis Research Group from 1995 to 2003 (Hayashi N., 2005, personal communication). In total, 10 143 patients have been enrolled and HCV-related HCC constituted 72.6% of cases. Among them, non-B non-C HCC accounted for 9.3%. In 946 patients with non-B non-C HCC, half of the cases were of unknown origin, and nonalcoholic steatohepatitis/diabetes mellitus caused only 5.4% in non-B non-C HCC.

#### **GEOGRAPHIC VARIATION IN LIVER CANCER AND HBV/HCV INFECTION**

Although Japan is a relatively small country with a homogenous population, the incidence of HCC varies greatly among different regions. The Vital Statistics of Japan for 2003 published in 2005 by the Japanese Ministry of Health, Labour, and Welfare on the incidence of deaths as a result of HCC in its 48 prefectures shows a gradient increase of death rates for HCC along the axis of Japan from east to west. The average age-adjusted death rate of HCC among 48 prefectures was 27.0 per 100 000 people (Fig. 5). Nationwide health screening for HBsAg and anti-HCV in the over 40 years of age population has been performed since 2002, and prevalence rates for these markers have been analyzed by each prefecture in Japan. In 2003, the average HBsAg prevalence and anti-HCV were 1.1 and 1.0%, respectively, in the total Japanese population (Fig. 5). There were highly significant associations between death rate from HCC in each prefecture and prevalence of anti-HCV (Fig. 6), but there was no correlation with the prevalence of HBsAg (Fig. 6). For instance, although Okinawa Prefecture has the highest prevalence rate of HBsAg (3.1%), death rate from HCC was the lowest (10.6/100 000 people). For an explanation on this discrepancy, HBV genotype Bj, which shows good clinical prognosis,<sup>11,12</sup> is the dominant source in Okinawa. In contrast, areas with high rates of anti-HCV, especially western Japan, had high death rates from HCC. HCV appears to be the major contributor to rates of primary liver cancer. Saga Prefecture shows the highest death rates in Japan (43.1/100 000), and the highest prevalence rate of anti-HCV (3.9%).

#### **ANTIVIRAL THERAPY SUPPRESSES INCIDENCE OF HCC**

As described above, HCV infection is a major cause of HCC in Japan, suggesting eradication of HCV contributes to the decrease in incidence of HCC and death rates from HCC. A summary of different studies on the incidence of HCC among patients with chronic hepatitis C who were treated with interferon in Japan is noted<sup>13-18</sup> (Table 1). These studies suggested a moderate decrease in the risk for HCC in patients with chronic hepatitis C treated with interferon. Especially, the reduction of incidence of HCC was more convincingly shown in patients with sustained virological response, compared with no responders and non-treated patients.

Between 1992 and 2001, approximately 300 000 patients with chronic hepatitis C had received interferon (IFN) monotherapy in Japan. As shown in Figure 1, it was remarkable that the numbers of deaths and the death rate from HCC decreased in 2003. These phenomena suggest that antiviral treatment reduces the risk of HCC in patients with HCV infection.

In cases of hepatitis B, Matsumoto *et al.*<sup>19</sup> reported that antiviral treatment with lamivudine might suppress the risk of HCC in patients with chronic hepatitis B by multicenter, retrospective study.

#### **CONCLUSION**

The numbers of deaths and death rates from HCC showed sharp increases beginning in 1975. However, the annual deaths (34 089) and death rate (27.0/100 000) from liver cancer decreased in 2003. Although both HBV and HCV

infections have a major role in HCC in Japan, HCV-related HCC represents 75% of all HCC in Japan. The incidence of HCC without HBsAg or anti-HCV accounted for 7–12% in Japan and half of non-B non-C-HCC was of unknown origin. Geographically, HCC is more frequent in western than eastern Japan, and the death rates of HCC in each prefecture correlate with prevalence of anti-HCV, but not with HBsAg prevalence. IFN therapy for chronic hepatitis C has reduced the risk factors for development of HCC, especially among patients with sustained response.

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**Figure 1** Changes in annual numbers of deaths of patients with primary liver cancer between 1958 and 2003, after data from the Vital Statistics of Japan, to which statistics are reported every year by the Ministry of Health, Labor, and Welfare.

**Figure 2** Changes in the death rate of primary liver cancer in males (&utri;), females (&blf;), and in total (&lzf;).

**Figure 3** Changes in mean ages of male (&blf;) and female (&blf;) patients with HCC between 1984 and 2001.

**Figure 4** Changes in etiology of HCC between 1990 and 2001. HBsAg+ (&blf;), anti-HCV+ (shaded gray), unknown and others (&blf;).

**Figure 5** (a) Death rates from primary liver cancer (per 100 000), total 27.0, (b) HBsAg prevalence, total 1.1%, and (c) anti-HCV prevalence, total 1.0% among people over 40 years of age in 48 prefectures in 2003.

**Figure 6** Relationships between death rate of primary liver cancer and prevalence of (a) HBsAg ( $r = 0.85$ ,  $P = 0.57$ ), and (b) anti-HCV ( $r = 0.67$ ,  $P < 0.0001$ ,  $y = 14.2x + 14.98$  among the general population over 40 years of age in 2003).

**Table 1** Summary of the findings in representative studies on the incidence of HCC among patients with chronic hepatitis C treated with interferon alone in Japan

Author	Untreated	Treated						
		No. HCC/ No. cases	%	Non-SVR		SVR		Total
				No. HCC/ No. cases	%	No. HCC/ No. cases	%	
Nishiguchi <i>et al.</i> <sup>13</sup>	17/45	38					2/45	4.4
Kasahara <i>et al.</i> <sup>14</sup>			41/709	5.8	5/313	1.6	46/1022	4.5
Imai <i>et al.</i> <sup>15</sup>	19/140	13					18/419	4.3
Ikeda <i>et al.</i> <sup>16</sup>	67/452	15	23/730	3.2	5/461	1.1	28/1191	2.4
Yoshida <i>et al.</i> <sup>17</sup>	67/395	17	214/1556	13.8	27/836	3.2	241/2392	10.1
Okanoue <i>et al.</i> <sup>18</sup>			119/849	14.0	8/397	2.0	127/1246	10.2
Total	170/1032	17	397/3844	10.3	45/2007	2.2	462/6315	7.3

SVR, sustained virological response

Figure 1

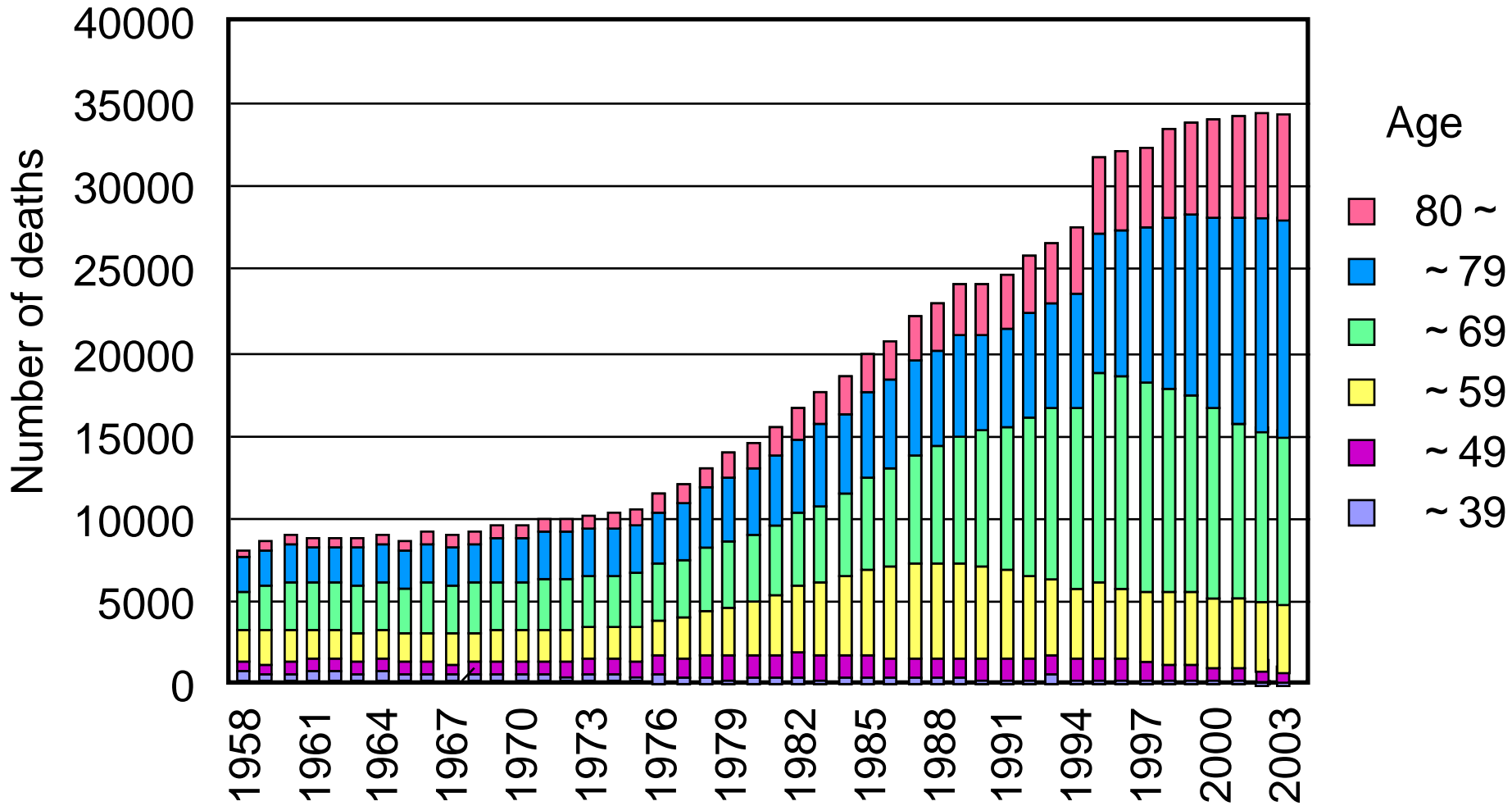


Figure 2

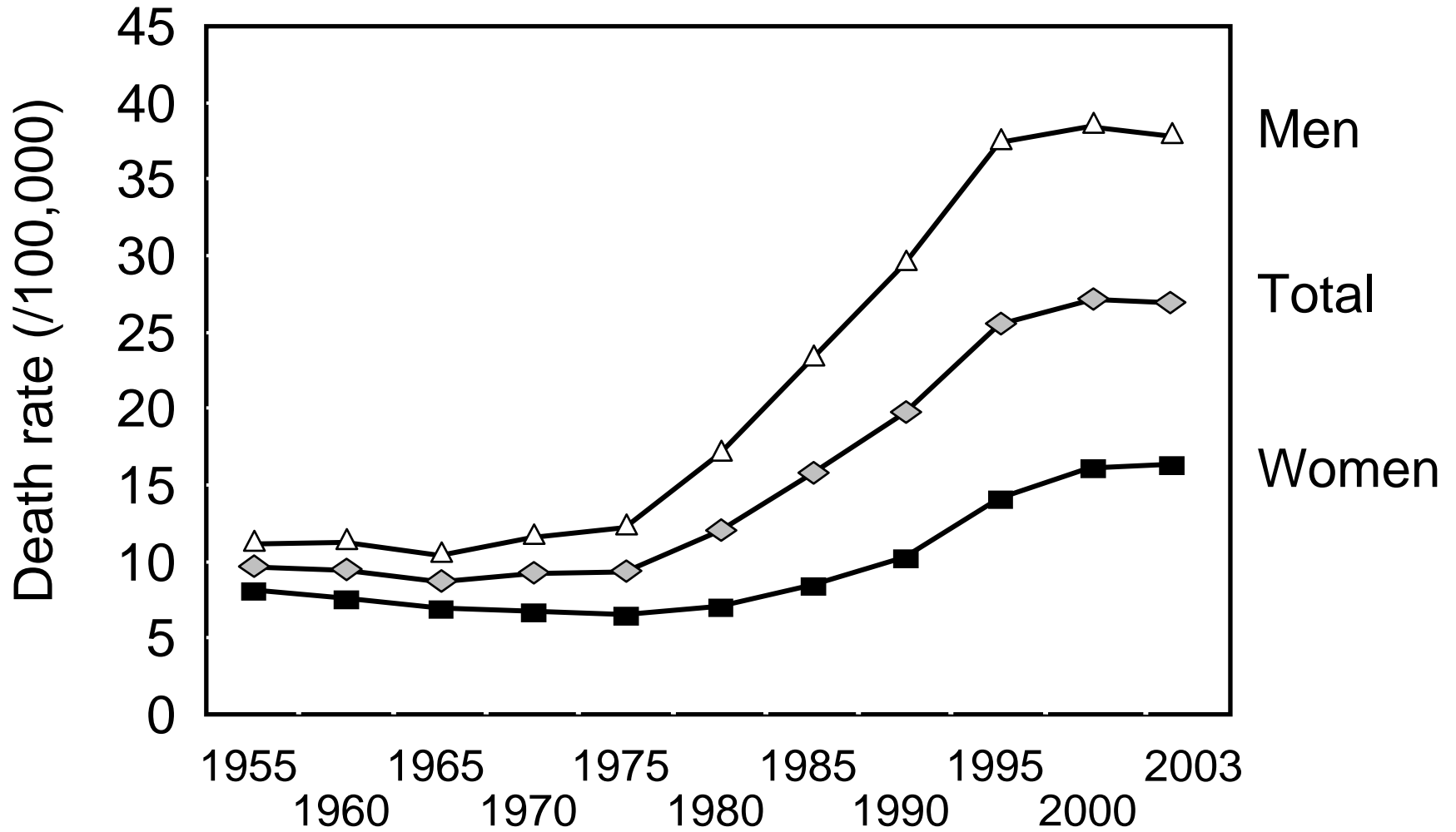


Figure 3

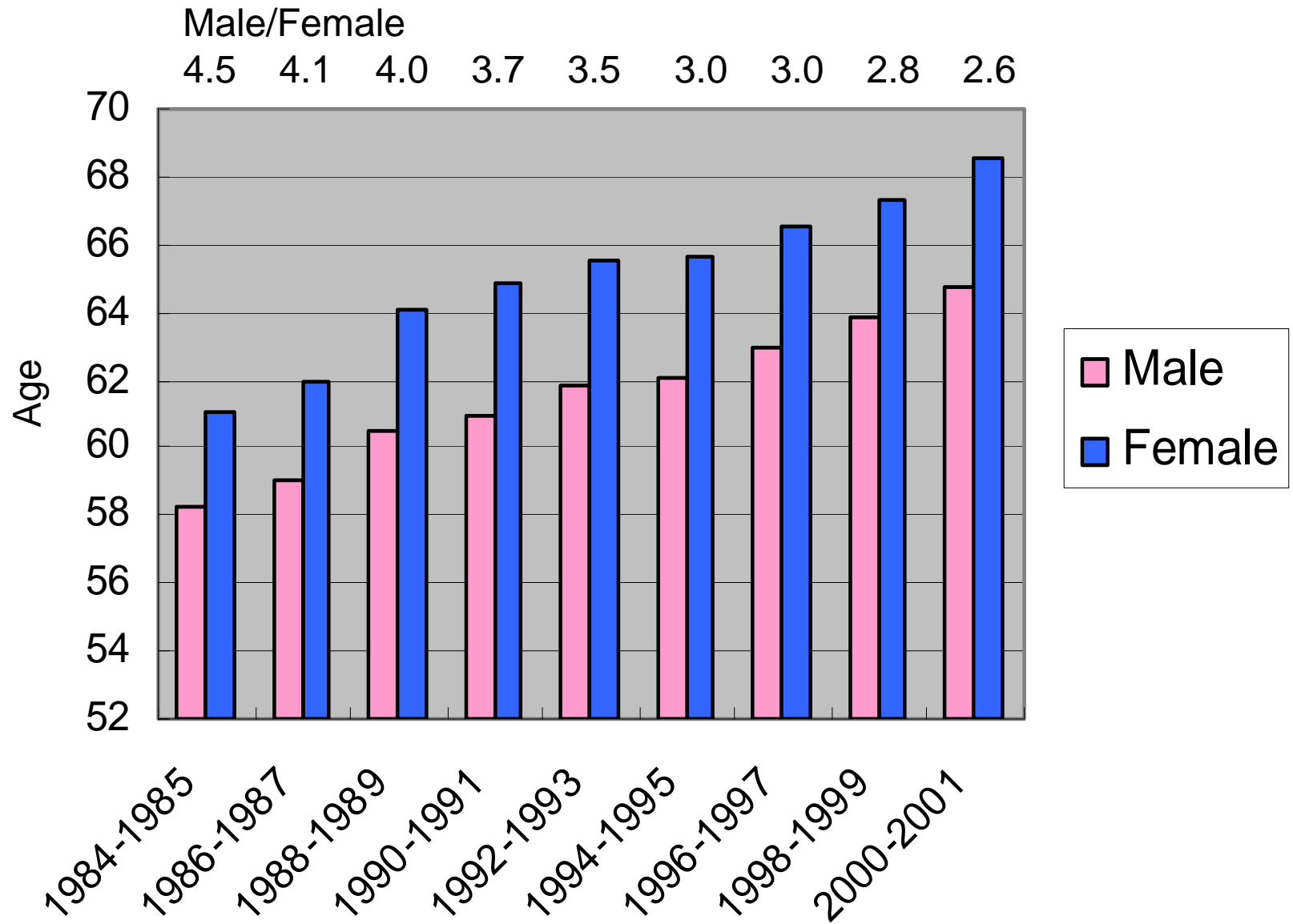


Figure 4

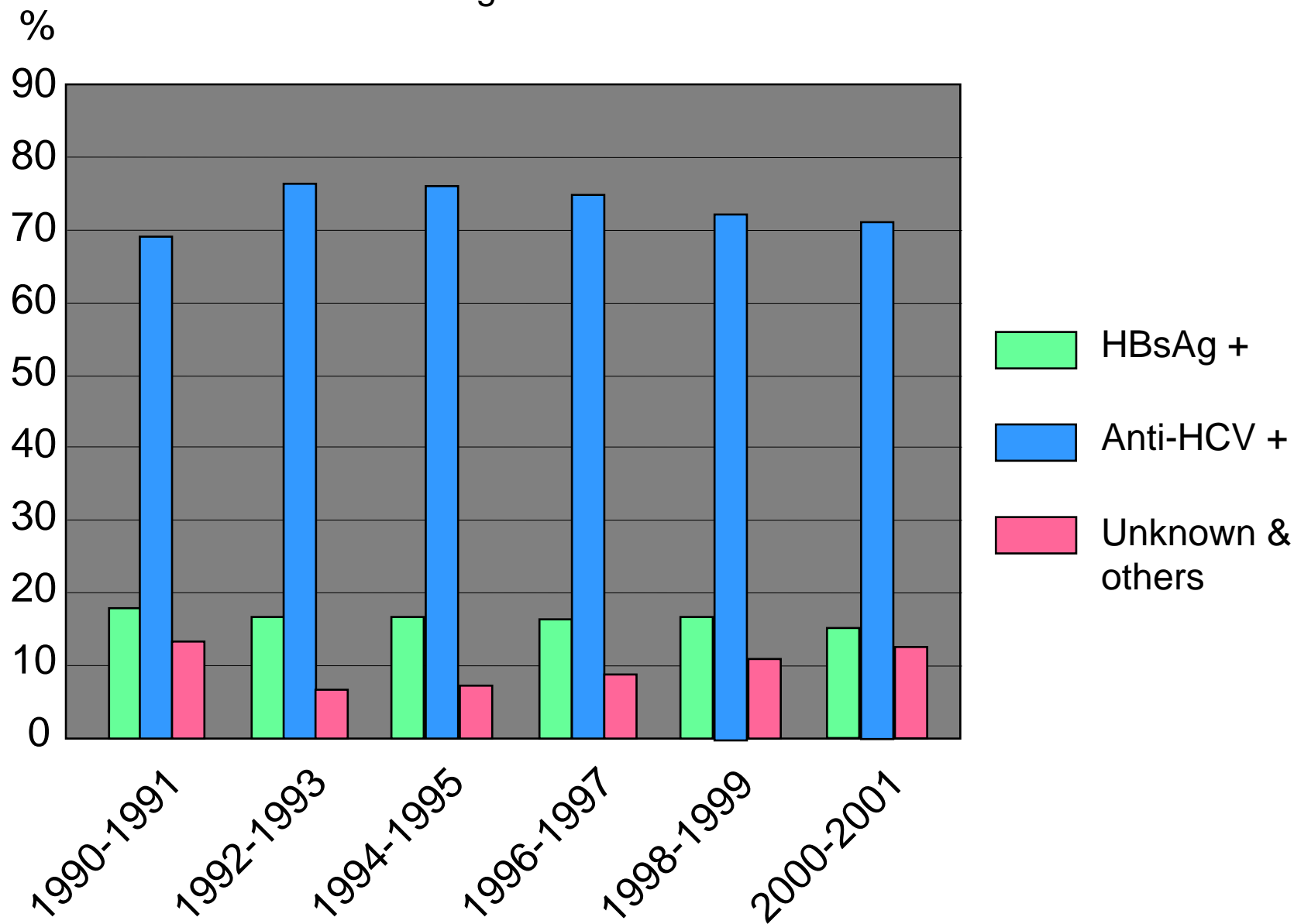
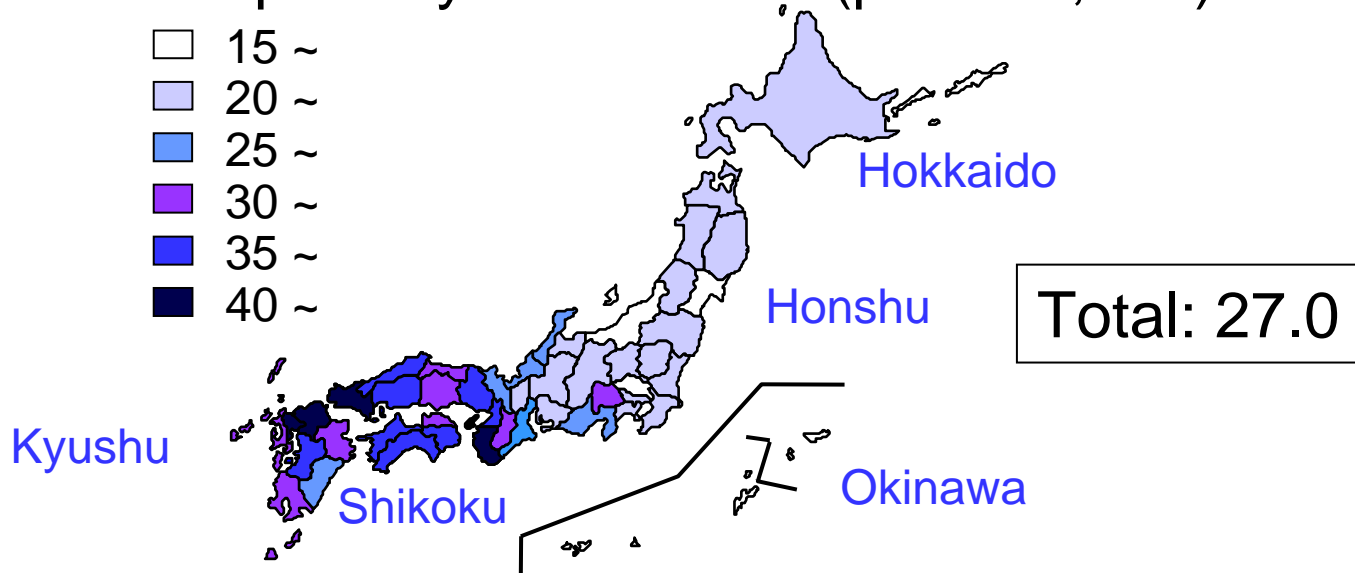
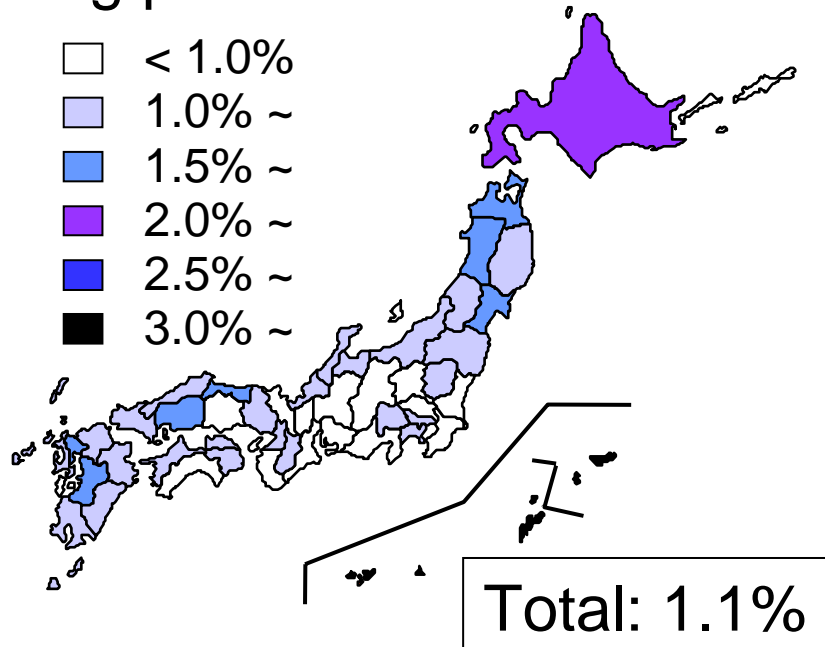


Figure 5

# Death rate of primary liver cancer (per 100,000) in 2003



## HBsAg prevalence



## Anti-HCV prevalence

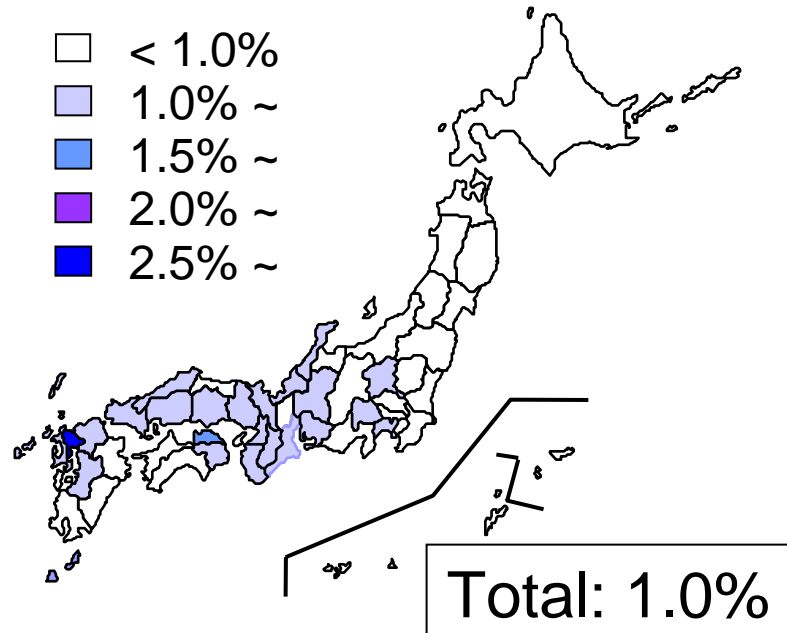
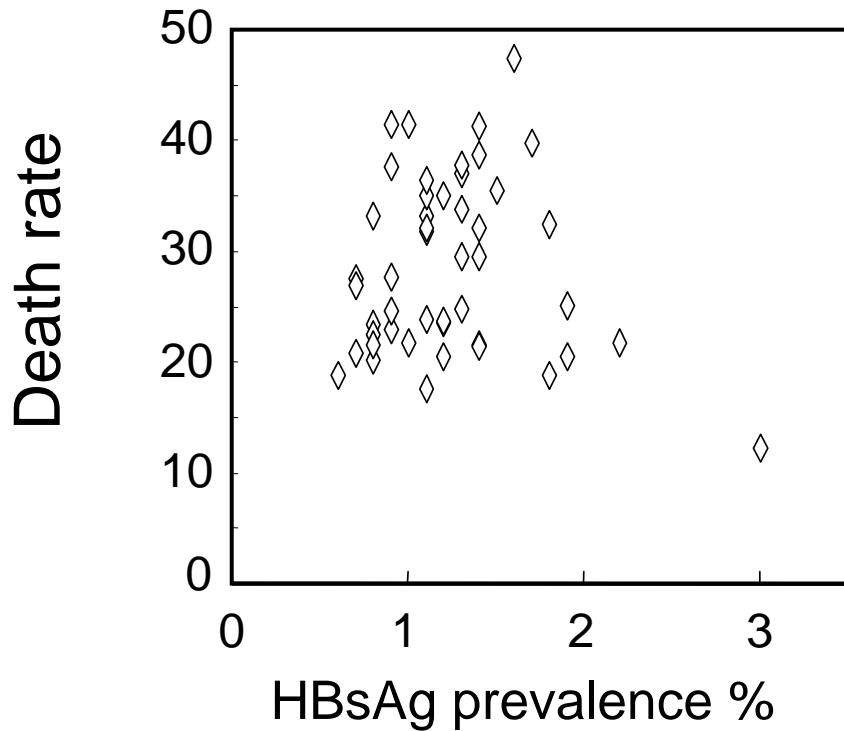




Figure 6

$r = -0.085, P = 0.57$



$r = 0.67, P < 0.0001$   
 $y = 14.2x + 14.98$

